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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/142,597	03/05/99	COWDEN W	120081.403

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 06/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/142,597	Applicant(s) Cowden et al.
	Examiner S. Devi, Ph.D.	Group Art Unit 1641

☒ Responsive to communication(s) filed on *05/11/2000.*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-28* is/are pending in the application.

Of the above, claim(s) *9-14 and 22-28* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8 and 15-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election

1) Acknowledgment is made of Applicants' election filed 05/11/2000 (paper no. 6), of invention I, claims 1-8 and 15-21, drawn to a therapeutic composition comprising a species of *Coxiella* or antigenic component(s) therefrom, and a method of preventing, inhibiting, delaying onset of or ameliorating the effects of an autoimmune disease in a mammal, in response to the restriction requirement mailed 01/05/2000 (paper no. 5). Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)).

Status of Claims

2) Claims 1-28 are pending.

Claims 9-15 and 22-28 are canceled via the paper filed 05/11/2000 (paper no. 6).

Claims 1-8 and 15-21 are under examination and a First Action on the Merits is issued on these claims.

Priority / Continuity

3) The instant application is a 371 of PCT/AU97/00161, filed 02/14/1997 and claims foreign priority to application, PN 8703, filed 03/14/1996 in Australia.

Drawings

4) The drawings submitted 03/05/99 are not objected to by the Draftsperson under 37 CFR 1.84 or 1.152 and as such, the drawings have been approved as formal drawings. A copy of the PTO 948 is attached to this Office Action (paper no. 7).

Abstract

5) This application currently does not contain an abstract of the disclosure as required by 37 C.F.R 1.72(b). However, as this application is filed under 371 with a priority claim to PCT/AU97/00161, a copy the published abstract from PCT/AU97/00161 is placed in the instant application as page number 31. If Applicants desired changes to the abstract, such changes should be directed to the abstract of the PCT/AU97/00161.

Specification - Informalities

6) The instant application is informal in the format or arrangement of the specification. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the Applicants' use.

Content of Specification

(a) Title of the Invention: See 37 C.F.R 1.72(a). The title of the invention should be placed at the top of the first page of the specification. It should be brief but technically accurate and descriptive, preferably from two to seven words.

(b) Cross-References to Related Applications: See 37 C.F.R 1.78 and M.P.E.P § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See M.P.E.P § 310.

(d) Reference to a "Microfiche Appendix": See 37 C.F.R 1.96(c) and M.P.E.P § 608.05. The total number of microfiche and the total number frames should be specified.

(e) Background of the Invention: The specification should set forth the Background of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(f) Brief Summary of the Invention: A brief summary or general statement of the invention as set forth in 37 C.F.R 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the

Rejection(s) under 35 U.S.C § 112, First Paragraph

7) Claims 1-8 and 15-21 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a therapeutic composition for inhibiting the occurrence of IDDM in a mammal, preventing the recurrence of insulin-dependent diabetes mellitus (IDDM) in a spontaneously diabetic mammal transplanted with syngeneic islet tissue, ameliorating the effects of IDDM and protecting beta cells from autoimmune destruction in a mammal, comprising a *Coxiella burnetii* QVAX vaccine or QFA antigen, and a method of using the composition (see Examples 1-5), does not reasonably provide enablement for prevention of any autoimmune disease using any *Coxiella* antigen and analogue and homologue thereof.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a therapeutic composition comprising antigenic components of *Coxiella burnetii*, or antigenic components "analogous or homologous" to one or more antigenic components of a species of *Coxiella* or *Coxiella burnetii*, and its use in a method for preventing, inhibiting, ameliorating or delaying the onset of the effects of an autoimmune disease, IDDM in particular. Although the relative skill of those in this art is high, the breadth of the claims encompasses any *Coxiella* antigen, or antigenic components analogous or homologous to one or more antigenic components of *Coxiella,* for use against any autoimmune disease. However, neither *Coxiella* antigens, nor antigenic components analogous or homologous to the antigenic components of a species of *Coxiella,* or *Coxiella burnetii* other than QFA or QVAX are identified, or enabled as a therapeutic composition for inhibiting the occurrence of any autoimmune disease or IDDM in a mammal, preventing the recurrence of any autoimmune

disease or IDDM in spontaneously diabetic mammal transplanted with syngeneic islet tissue and protecting beta cells from autoimmune destruction in a mammal. The only working examples are to QFA and QVAX, both antigenic components of *Coxiella burnetii*. Though any composition containing QFA would likely to work similarly to QFA, one skilled in the art would not expect every *Coxiella* antigen to work. No further guidance is given as to what other antigens would and would not work.

The art, as applied below, teaches a specific mycobacterial antigenic component that is analogous or homologous to an antigenic component of *Coxiella burnetii* and demonstrates that such a mycobacterial component is effective in treating IDDM. See paragraph 11 below. The claims as drafted currently, encompass non-mycobacterial antigenic components analogous or homologous to *Coxiella burnetii* antigenic components and a method of using the same for treating, preventing, ameliorating, inhibiting or delaying onset of the effects of any autoimmune diseases including IDDM. However, the parameters for determining the analogousness or homologousness of one antigen relative to another are not disclosed. Furthermore, there is no evidence in the instant specification showing that any antigenic components analogous or homologous to any antigen(s) of a species of *Coxiella,* or *Coxiella burnetii,* other than QFA and QVAX, do indeed prevent, treat, inhibit, delay onset of, or ameliorate the effects any autoimmune disease including IDDM. Without specific identification and disclosure of the production of non-mycobacterial antigenic components that are analogous or homologous to the antigenic components of *Coxiella burnetii* and without a demonstration of, or specific guidance as to using such antigenic components for preventing, inhibiting, delaying onset of, or ameliorating the effects of sufficiently representative numbers of *Coxiella*- or non-*Coxiella*-induced autoimmune diseases including IDDM, one of ordinary skill in the art would not be able to make and use the therapeutic composition for the recited method or purpose and therefore, would not be able to reproducibly practice the claimed invention without undue experimentation. Given the lack of guidance in the specification and since treating, inhibiting, preventing, delaying onset of, or ameliorating the effects any autoimmune diseases, or IDDM in particular, with any non-*Coxiella* or non-mycobacterial antigenic components, is not predictable, one of ordinary skill in the art could not make or use the broadly claimed invention, without undue experimentation. The claims are viewed as not meeting

the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

8) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

9) Claims 1-8 and 15-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 3 lacks proper antecedence for the recitation "the autoimmune condition" (see line 1). Claim 3 depends from claim 2, which is turn depends from claim 1. Claim 1 recites "an autoimmune disease" (see line 2), but not an autoimmune "condition". Therefore, for proper antecedence, it is suggested that Applicants replace the recitation "the autoimmune condition" in line 1 of claim 2 with --the autoimmune disease--.

(b) Claims 1 and 15 are vague in the recitation "analogous" or "homologous" components, because it is unclear what is encompassed in these limitations. Since the parameters for determining the analogy or homology of one antigen relative to another are not defined, it is not clear what constitutes analogous or homologous components.

(c) Claims 2-8 and 16-21 stand rejected under 35 U.S.C. § 112, second paragraph, because of the defect(s) in the base claim(s) identified above in subparagraphs (a) and (b).

Rejection(s) under 35 U.S.C. § 103

10) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

11) Claims 1-8 and 15-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Qin *et al.* (*J. Immunol.* 150: 2072-2080, 1993) in view of Vodkin *et al.* (*J. Bacteriol.* 170: 1227-1234, 1988), Edgington (*Biotechnology* 13: 1442-1444, 13 December 1995) and Barnes *et al.* (WO 87/06590).

Qin *et al.* teach a therapeutic composition comprising an emulsion of CFA or complete Freund's adjuvant, for treating or preventing the development of type I diabetes (i.e., IDDM) in non-obese diabetic (NOD) mice, i.e., laboratory mammalian test animals. CFA contains the adjuvanting cell wall of *Mycobacterium* strain, H37Ra (i.e., *M. tuberculosis*) (see abstract; the paragraph bridging pages 2072 and 2073, and the second paragraph under 'Materials and Methods'). The antigenic component is contained in saline, i.e., a pharmaceutically acceptable carrier or diluent (see second paragraph under 'Materials and Methods'). Qin *et al.* also teach that CFA treatment prevents the adverse effects, or the autoimmune destruction of transplanted syngeneic islets in diabetic NOD mice (see page 2073, left column, lines 4-6). Qin *et al.* do not teach that the antigenic component contained in CFA is "analogous or homologous" to an antigenic component of *C. burnetii*.

However, Vodkin *et al.* teach an immunogenic heat shock protein (HSP) antigen (i.e., the antigenic component) of *Coxiella burnetii*, which is "homologous" to a hsp (heat shock protein) polypeptide of mycobacterial species including *M. tuberculosis,* and its potential as an efficacious vaccine (see abstract, and the third full paragraph in the left column on page 1230). The protein is immunogenic in mice, elicits antibodies against *Coxiella burnetii* and is suggested as a subunit vaccine against Q fever (see the last paragraph under 'Discussion'). Vodkin *et al.* also disclose a whole cell lysate (i.e., QFA) of *C. burnetii* that contains the homologous antigenic component (see page 1230, second full paragraph, and Figure 7).

Edgington teaches that Freund's complete adjuvant (i.e., CFA) contains a mixture of highly conserved mycobacterial hsps (see page 1443, left column, first full paragraph). Edgington

discloses that hsps serve as natural stand-alone adjuvants (see page 1443, last paragraph). Edgington also teaches that the "general opinion that links hsps to diabetes ... is simply uninformed" (see abstract, and page 1443, left column, first full paragraph).

Barnes *et al.* disclose the disadvantages of using Freund's complete adjuvant for *in vivo* use. Barnes *et al.* teach that when used with an antigen in an injectable form, large lesions often form at the site of injection, which render the adjuvant unsatisfactory for use in humans, pets and in meat animals (see page 1, fourth full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace Qin's CFA with Vodkin's immunogenic *Coxiella burnetii* HSP antigenic component, or the *Coxiella burnetii* whole cell preparation or lysate, to produce the composition and the method of the instant invention, with a reasonable expectation of success, because CFA is known in the art to contain highly conserved mycobacterial hsps as taught by Edgington, and mycobacterial hsps are known in the art to be homologous to the *Coxiella burnetii* antigenic HSP component as taught by Vodkin *et al.* Given the art-recognized adjuvanting function of highly conserved bacterial hsps and the knowledge that these hsps are not linked to the pathogenesis of diabetes as taught by Edgington, one skilled in the art would be motivated to produce the instant invention for the expected benefit of avoiding the art-recognized undesired large lesions associated with Qin's CFA. Further, substitution of one immunogenic hsp antigenic component with another, homologous, functionally equivalent, conserved, antigenic hsp component would be obvious to a skilled artisan and would be expected to bring about similar beneficial results or effects.

Claims 1-8 and 15-21 are *prima facie* obvious over the prior art of record.

12) Claims 1, 2, 15, 16, 20 and 21 are rejected under 35 U.S.C § 102 (b) as being anticipated by Zhang *et al.* (*Acta Virologica* 38: 327-332, 1994), or Gajdosova *et al.* (*Acta Virologica* 38: 339-344, 1994), each in view of Levy *et al.* (*Eur. J. Epidemiol.* 5: 447-453, 1989, abstract), or Roue *et al.* (*Lancet* 341: 1094-1095, 1993).

Zhang *et al.* teach a composition comprising a purified outer membrane protein of *Coxiella burnetii* (i.e., an antigenic component) and its potential use as a subunit vaccine. The protein is contained in an adjuvant or a pharmaceutically acceptable carrier and is administered to mice and guinea pigs (i.e., laboratory mammalian test animals). The composition elicits both B-cell and T-

cell mediated immunity in mice and guinea pigs and confers protection against challenge with *Coxiella burnetii* (see abstract; page 328, left column; Table 2 and Figure 2). Zhang *et al.* also teach the use of a suspension of killed phase I whole cell vaccines of *Coxiella burnetii* (i.e., QFA) in humans and animals (see page 327, left column).

Gajdosova *et al.* teach a composition comprising phase I *Coxiella burnetii* whole cells or Cb I (i.e., QFA) and/or outer membrane components of *Coxiella burnetii* contained in a pharmaceutically acceptable carrier. A method of administering the compositions to mice, i.e., laboratory mammalian test animals, for induction of protective humoral and cellular immunity is taught (see abstract; 'Materials and Methods' and 'Discussion'). Mice immunized with Cb I and an ONPC, i.e., a phase I trichloracetic extract (i.e., an antigenic component of *C. burnetii*), conferred highest degree of protection or resistance against challenge with *Coxiella burnetii* (see abstract and page 343, left column, second full paragraph).

Zhang *et al.* or Gajdosova *et al.* do not expressly teach their composition or the method for preventing, inhibiting or ameliorating an autoimmune disease in a mammal.

However, Levy *et al.* teach the association between Q fever and autoimmune disorder by providing serological evidence of existence or development of autoimmune antibodies (see abstract).

Similarly, Roue *et al.* teach that acute Q fever is associated with autoimmune disorders and development of autoimmune serological markers (see entire document, especially last paragraph).

Given the art recognized association between Q fever or coxiellosis and autoimmune manifestations as taught by Levy *et al.* or Roue *et al.*, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Gajdosova's or Zhang's therapeutic composition and method for preventing or ameliorating Levy's or Roue's autoimmune Q fever to produce the composition and the method of the instant invention, with a reasonable expectation of success. Since certain manifestations of Q fever are viewed as autoimmune disorders as taught by Levy *et al.* or Roue *et al.*, one skilled in the art would be motivated to extend the use of Gajdosova's or Zhang's therapeutic composition and the method for the purpose of also preventing or ameliorating the autoimmune effects of Q fever, with a reasonable expectation of success.

Claims 1, 2, 15, 16, 20 and 21 are *prima facie* obvious over the prior art of record.

Objection(s) to Claim(s)

13) Claims 1 and 15 are objected to for the reason explained below:

In claims 1 and 15, it is suggested that Applicants delete the recitation "otherwise" (see line 1 of claim 1 and line 2 of claim 15) as it is superfluous or unnecessary.

Prior Art

14) The prior art made of record and not relied upon currently in any rejection is considered pertinent to Applicants' disclosure:

- Ackland *et al.* (*Med. J. Austral.* 160: 704-708, 1994) disclose a vaccine composition comprising killed whole cells of *Coxiella burnetii* and a method of immunizing humans with the composition that conferred 100% immunity to Q fever (see abstract).
- Stchepinsky *et al.* (*Arch Mal. Coeur. Viass.* 88: 511-515, April, 1995) teach that certain chronic and complex *Coxiella burnetii* infections represent an autoimmune disease (see abstract).
- Kayser *et al.* (*Respiration* 62: 114-116, March 1995) teach that clinically, histologically and immunologically, Q fever due to *Coxiella burnetii* is associated with changes in the immune system comparable to autoimmune reactive diseases (see abstract).
- Tobin *et al.* (*Am. J. Med.* 72: 396-400, 1982) teach a phase I complement fixing antigen of *C. burnetii* (see abstract).
- Elias *et al.* (*PNAS* 87: 1576-1580, 1990) teach a method of ameliorating or preventing insulin-dependent diabetes mellitus (IDDM) in non-obese diabetic or NOD mice by administering a composition comprising a cross-reactive antigenic component, *M. tuberculosis* hsp65, in phosphate buffered saline or PBS (i.e., pharmaceutically acceptable carrier or diluent) (see the paragraph bridging left and right columns on page 1578 and the first three full paragraphs in the right column; and the last paragraph under 'Discussion' on page 1579).
- Toyota *et al.* (*Diabetes* 35: 496-499, 1986) teach a method of protecting NOD mice from developing type I diabetes by administering a potent bacterial immunomodulator comprising a cellular preparation of streptococcal cells, OK-432 (see title and abstract). Toyota *et*

al. teach that immunomodulator may protect NOD mice from developing diabetes (see page 496, right column).

Remarks

15) Claims 1-8 and 15-21 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1641 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 a.m. to 4.00 p.m. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD
S. Devi
Patent Examiner
June 2000